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EXAMINER	
NGUYEN, D	
ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 05/11/98

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary	Application No. 08/799,910	Applicant(s) Falb et al.
	Examiner Dave Nguyen	Group Art Unit 1633

☒ Responsive to communication(s) filed on *Sep 5, 1997*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *70-96* is/are pending in the application.

Of the above, claim(s) *90-96* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *70-89* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5 and 6*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

The specification has been amended, claims 1-69 have been canceled, and claims 70-96 have been added by the preliminary amendment filed September 5, 1997.

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I. Claims 70-89, drawn to an isolated nucleic acid encoding a fchd605 amino acid sequence, vectors, and host cells, classified in Class 536, subclass 23.5; Class 435, subclasses 320.1, and 325, respectively.

Group II. Claims 90-96 drawn to an isolated fchd605 polypeptide, classified in Class 530, subclass 388.23.

The inventions are distinct, each from the other because of the following reasons:

Groups I and II are directed to products that are district both physically and functionally, and are therefore patentably distinct; and are not required one for the other. For example, the polynucleotides of Group I and VI are a fundamentally different type of molecule than the polypeptides of Group II, and the polynucleotides for Group I can be used other than to produce the protein of Group II; for instance, it can be used as a probe in nucleic acid hybridization. Thus, Groups I and II are directed to physically and functionally distinct elements, and are therefore patentably distinct; and are not required one for the other.

During a telephone conversation with Attorney Jonathan Klein on May 1, 1998, a provisional election was made with traverse to prosecute the invention of claims 75-89.

Affirmation of this election must be made by applicant in responding to this Office action. Claims 90-96 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 84-87 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims, absent the qualifying language of "isolated" or cultured *in vitro* include in its scope a human containing the cells transformed with vectors containing nucleotide sequence of claims 70-76. A claim including within its scope a human being is not considered patentable subject matter as the limited but exclusive property right in a human being is barred by the United States Constitution. See 1077 OG 24.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 70-89 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention in the presently claimed nucleic acids.

The claimed invention is directed to an isolated polynucleotide encoding SEQ ID NO:10. The claims also recite an isolated polynucleotide having SEQ ID NO: 9, and variants thereof. Further, the claimed invention is directed to DNA sequences that hybridize "under moderately stringent conditions" and/or "under highly stringent conditions" to the polynucleotide sequences of claims 70 and 74, *e.g.,* SEQ ID NO: 10. The application indicates that fluid shear stress is thought to be responsible for the prevalence of atherosclerotic lesions in areas of unusual circulatory flow (p. 25). The application demonstrates the use of shear stressed endothelial cell paradigm (Section 5.1.1.6, p. 25) to identify, isolate, and sequence genes which are differentially expressed in exposed versus control cells, *e.g.,* isolation of SEQ ID NO: 9, and its encoded polypeptide, SEQ ID NO: 10 (referred as fchd605). The application indicates that the fchd605 produced a 1.5kb mRNA that is unregulated after 5 hours treatment with oxidized LDL, and to a lesser degree with native LDL, as compared to untreated monocytes, and that based on sequence

analysis, the fchd605 gene product has similarity to the mouse gly96 gene, which encodes a cytokine inducible glycosylated protein expressed in mouse lung, testes, and uterus (p. 118). The application discloses the use of fchd605 and variants in: identifying and isolating novel sequences (pp 40, and 47; as a probe); producing antibodies capable of specifically recognizing one or more differentially expressed or pathway gene epitopes, such antibodies may be used, for example, in the detection of a fingerprint, or in the method for the inhibition of abnormal target gene activity (p. 57), or in the diagnosis of cardiovascular disease by *in vivo* techniques (p. 106); producing the founder lines of transgenic animals (p. 62); in screening assays (p. 67-72), in treating cardiovascular diseases (p. 85), and in screening for ligands of the fchd605 gene product and antagonists of fchd605 gene product-ligand interaction (p. 132). However, the specification does not teach one skilled in the art how to use the fchd605 gene without first having to perform undue experimentation to identify the biological function of the fchd605 gene product. The specification merely indicates that the fchd605 end product is up-regulated in shear stress treatment, has similarity to the mouse gly96 gene, which encodes a cytokine inducible glycosylated protein expressed in mouse lung, testes, and uterus (based on homology comparison to known sequences). However, since the nucleic acid sequence encoding a particular protein determines the protein's structural, immunogenic and functional properties, predictability of which changes can be tolerated in the nucleic acid sequence and still retain similar immunogenicity and functionality of the protein requires a knowledge of and guidance with regard to which amino

acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly intolerant to modification), and detailed knowledge of the ways in which a protein's structure relates to its immunogenic determinants and functional usefulness. Thus, it is not apparent what is biological activity of the fchd605 gene product, particularly since it is known in the art that there are many gene products which are up-regulated in shear stress treatment (see Gura, Science, Vol. 269, 1995). Furthermore, the problem of predicting protein structure from mere sequence data of a single amino acid or nucleic acid sequence and in turn utilizing predicted structural determinations to ascertain functional aspects of the fchd605 and finally what changes can be tolerated with respect thereto is complex and unpredictable. The application also demonstrates that the fchd605 gene is differentially expressed in shear stress exposure. However, the application fails to provide a reasonable correlation between the induction of expression of the fchd605 gene and its biological activity as a cytokine inducible glycosylated protein. Without guidance, it would require undue experimentation to determine the biological role of the fchd605 gene product, particularly given the Papadaki *et al.* reference (Biotechnol. Prog., 13:209-221, 1997) disclosing that many genes differentially expressed during shear stress exposure in *in vitro* studies are involved in a number of biological pathways and are associated with a number of distinct biological activities, *e.g.,* mehano-receptors, protein kinases, transcription factors, G-protein receptors (which is known to belong to a large family of G-protein receptors wherein each member of the family exhibits a specific biological function), Tyrosine kinase receptors, and

channel proteins, and that there is a complex interplay of shear stress-induced signal transduction and gene regulation in vascular cells (p. 219).Furthermore, a simple analysis of primary and secondary structures of an unknown protein based on sequence analysis is not well correlated with the functional activity of the encoded DNA product because the relationship between the amino acid sequence of a polypeptide and its tertiary and/or quaternary structure is not well understood and is not invariably predictable and is not predictable; and , thus, it is not apparent how one skilled in the art arrives at functionally active polypeptides encoded by the claimed nucleic acid sequences without undue experimentation. See Ngo *et al.*, in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz *et al.*, (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495).

Regarding the claimed invention directed to isolated DNA sequences that hybridize "under moderately stringent conditions" and/or "under highly stringent conditions" to the polynucleotide of claims 70 and 74, *e.g.*, DNA sequence encoding SEQ ID NO: 10, the state of the prior art as exemplified by Wallace *et al.* (Methods in Enzymology (1987), 152:432) and Sambrook *et al.* (Molecular Cloning (1989), CSH:11.47) is such that determining the specificity of hybridization polynucleotides is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Furthermore, there is no guidance in the specification that discloses as to what the target sites in the protein are or what modifications can be made while retaining functional limitation. Furthermore, since the claims, *e.g.*, claim 72, recites no limitation on the

size of the claimed polynucleotide, said nucleotide encompasses any random sequence of any length, *e.g.*, length of 2 nucleotide residues. Since the structural limitations of the claim clearly cover an enormous number of polynucleotides and in view of the empirical and unpredictable nature of the art and lack of guidance with respect to appropriate modifications, one skilled in the art would have to make and test all nucleic acids that meet the structural limitations to determine which also meet the functional limitation. This amount of experimentation would be impossible in many lifetimes. Thus, it is not apparent how one skilled in the art determines which of the isolated polynucleotides that hybridize "under moderately stringent conditions" and/or "under highly stringent conditions" to the polynucleotide of claims 70 and 74 exhibit a biological activity without undue experimentation, particularly since neither SEQ ID NO: 9 nor SEQ ID NO:10 is enabled, and since the length of claimed sequences as recited in claims 72 and 75 is neither defined in the application nor in the claims. Therefore, based on the empirical and unpredictable nature of the invention and state of the art, the limited guidance and working examples in the specification, and the extensive quantity of experimentation needed to identify the polynucleotides encompassed by the claims, it would require an undue amount experimentation to make and use the polynucleotide sequences as recited in the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112, second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the application regards as his invention.

Claims 70-89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 70, 71, 74, and claims dependent thereto are indefinite in the recitation of "which is the complement of (a)" since it is not clear whether or not the complement is directed to a polynucleotide sequence which encodes a polypeptide wherein the polynucleotide sequence is the complement of the polynucleotide sequence set forth in (a), or is directed to an antisense sequence. If the latter is the case, it is not apparent which strands of the polynucleotide sequence of (a) are complement to the polynucleotide sequence of (b). Furthermore, the claims are in Markush format but the polynucleotide sequence set forth in (b) does not possess any of the functional properties set forth in (a), *e.g.,* directed to the identically encoded polypeptide.

Claims 84-87 are indefinite since the term "a genetically engineered host cell" does not distinguish over naturally occurring cells or cells implanted in an animal host, particularly since the polynucleotide in association with exogenous regulatory elements is not distinguishable over natural sequences contained in the naturally occurring cells or in cells implanted in a host animal. Furthermore, it is not apparent what are the metes and bounds of the "a nucleotide regulatory element exogenous to the polynucleotide" since the exogenous regulatory element encompasses natural adjacent sequences to the polynucleotide contained in the naturally occurring cells. Note

the specification at page 54 does not provide a closed language for the metes and bounds of the "exogenous nucleotide sequences".

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> a person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 72, 73, 75-89 are rejected under 35 U.S.C. 102(a) as being anticipated by, or in the alternative, under 35 U.S.C. 103(a) as being unpatentable over The WashU-Merck EST Project (published January 10, 1996, AN: N32077, embl-est Database).

Claims 72 and 75 are directed to isolated nucleic acid sequences that hybridize under highly stringent conditions to the polynucleotide of claims 70 and 74, *e.g.,* SEQ ID NO: 9. Claim 73 is directed to an isolated nucleic acid that hybridizes under moderately stringent conditions to the polynucleotide of 70, *e.g.,* SEQ ID NO: 9. Claims 77-89 are drawn to isolated vectors and

host cells containing the nucleic acid of claims 72, 73, and 75. The WashU-Merck EST Project discloses a polynucleotide sequence isolated from a cDNA clone which is 96.4% identical to a DNA segment consisting of nucleotide residues 5-550 of SEQ ID NO: 9. Absent evidence to the contrary, and in the alternative, the polynucleotide sequence of The WashU-Merck EST Projects has all of the properties cited in the claims, *e.g.,* "hybridizes under highly stringent conditions".

Claims 72, 73, 75-89 are rejected under 35 U.S.C. 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. 103 as being unpatentable over The WashU-Merck EST Project (published February 8, 1995, AN: T49532, embl-est Database).

Claims 72 and 75 are directed to isolated nucleic acid sequences that hybridize under highly stringent conditions to the polynucleotide of claims 70 and 74, *e.g.,* SEQ ID NO: 9. Claim 73 is directed to an isolated nucleic acid that hybridizes under moderately stringent conditions to the polynucleotide of 70, *e.g.,* SEQ ID NO: 9. Claims 77-89 are drawn to isolated vectors and host cells containing the nucleic acid of claims 72, 73, and 75. The WashU-Merck EST Project discloses a polynucleotide sequence isolated from a cDNA clone which is 96.3% identical to a DNA segment consisting of nucleotide residues 1-403 of SEQ ID NO: 9. Absent evidence to the contrary, and in the alternative, the polynucleotide sequence of The WashU-Merck EST Project has all of the properties cited in the claims, *e.g.,* "hybridizes under highly stringent conditions".

Claims 70, 72, and 73-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillier *et al.* (Swiss-prot35 Database, published Feb., 1995, AC: P46695) taken with Fuller *et al.* (IDS).

Claim 70 is directed to a polynucleotide sequence encoding a polypeptide having the fchd605 amino acid sequence set forth in SEQ ID NO: 10. Claims 72 and 74 are directed to isolated nucleic acid sequences that hybridize under highly stringent conditions to the polynucleotide of claims 70 and 74, *e.g.,* SEQ ID NO: 9. Claim 73 is directed to an isolated nucleic acid that hybridizes under moderately stringent conditions to the polynucleotide of 70. Claims 77-89 are drawn to isolated vectors and host cells containing the nucleic acid of claims 72, 73, and 75. Hillier *et al.* disclose an isolated radiation-inducible immediate-early gene IEX-1 which is 98.9% identical to SEQ ID NO: 10. Given that it is known in the art that DNA recombinant techniques are employed to construct polynucleotide sequences encoding the gene product of Hillier (see Fuller *et al.,* for example), it would have been obvious for one of ordinary skill in the art to employ DNA recombinant techniques to construct DNA sequences encoding the glycoprotein of Hillier *et al.* and to employ the DNA sequences for gene expression in cultured cell lines, particularly since production of large amount of recombinant glycoproteins of Hillier is useful to study the protein activity as radiation-inducible proteins.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasmine Chambers may be reached at **(703)308-2035**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen

May 8, 1998

Christopher S. F. Low

CHRISTOPHER S. F. LOW
PRIMARY EXAMINER
GROUP 1800/600